December 24, 1952
[Second reply to your last,
dated Dec. 8 '52]

Dear Norton:

First let me send you best wishes for the season and the approaching new year.

The old one, 1951, does not leave without a minor headache, namely that I grossly underestimated reprint requirements for "Genetic exchange in Salmonella". Originally I ordered 650 which seemed a sufficient number, and would have been ordinarily. Of these, you should have received 200 by now. About two months ago, I realized this would be inadequate and asked to increase the order, but the type had already been killed! In order to fill my regular mailing list, I would need 75 (minimum) to 175 (max.) over the 25 still left from the first mailing. Obviously, I will not be able to fill the postcard requests as I had hoped, and must forward these to you. On the other hand, many of your own requests may duplicate my list. Unless you have as many as 400, it would be simpler for you to send your list to me than vice versa. If I may make a suggestion, you might have your secretary make out the address labels for <u>all</u> the reprints you planned to send out, but forward these to me for checking. I will mark the names already on my mailing list and return it to you. In no way to I can arrange to have a complete listing made, in duplicate, for future reference. My experience has been that if any list is to be kept at all, it has to be done this elaborately. I am sorry now not to have arranged to send out all the reprints from one address--it would have been much simpler, but it's too late now. I am going to inquire into the costs of a photo-offset reprinting, and if these are not prohibitive, will try to arrange to get several hundred more. As already mentioned to you, this reprint is not included in mailings to Rockefeller itself [except I notice that McCarty slipped by]. I hope I can rely on a sufficient supply to furnish copies to: Dubos, Goebel, Hotchkiss, Maramorosch, Braun, Horsfall--all I can remember off hand. There will be a comparable situation with the Cell Genetics review, but there was no helping this. You should get your kopy over the weekend.

There are some more interesting things to talk about. I wonder if it isn't time for us to start thinking about collecting the diverse evidence for the identification of FA with phage for publication as a second collaborative paper. There are a number of approaches to this problem all pointing to the same direction, but we have to be careful of the rigor of each. The consistency of the whole story has, I know, tended to make me a bit careless about polishing each angle of each individual approach. I suggest then that we start collecting the detailed evidence so that we can go over it critically and decide what more needs to be done. One item that does need cleaning up is the identification of the receptor. One anomaly is S. paratyphi A: Bruce has picked up an O mutant which can be transinduced by PLT22/2. I can confirm this, but the efficiency is <u>very</u> low. The rate of adsopption of phage will have to be checked, as well as the presumed absence of $XII_2$. On the other hand, I have an excpptional paratyphi A from Kauffmann which does carry $XII_2$, and it should adsorb PLT22. A second peculiarity appears in Boyd's work. PLT22 appears to be in his A1 group.

Boyd records A1 as lysing S. bovis-morbificahs! I could not confirm this with any of our b-m (and his A1 or PLT22), and Boyd's own strain died out. He is checking some others to see if this can be confirmed, in his own hands. I should not be too surprised if he was following a second, rough,phage in this case. I don't know the status of S. abortus-bovis anent XII$_2$, but will check this at Chamblee. Another approach is to block the receptor (preferably in extracts) with antibody. Spicer is setting this up, especially the more amusing experiment whether anti-IV will block XII of IV-XII complexes (and presumably not of IX-XII). He is also trying somatic transductions, has some reconstructions that make the technique promising, but so far has succeeded mostly in consuming a good deal of serum.

I will assume that you have nailed down the quantitative equivalence of phage and FA in filtration, adsorption to bacteria, and inactivation by serum. In a sense these would show that phage and FA are enclosed in the same kind of skins, but whether they are cohorts under the skin would still be unsettled. How about the rates of thermal inactivation and of differential centrifugation to clinch this end of it?

Let me give a quick rundown on some of our more recent experiments.

First,UV effects. All this is on PLT22 adapted to SW543 strains (still uncertain whether this is a mutative adaptation)-- "22B". Heavy doses (20 mins) knock the plaque forming ability from ca. $10^9$ to ca. $10^2$/ml. I cahbot demonstrate multiplicity reactivation of the heavily irradiated phage, perhaps because I can't get away from it. FA initially ca $10^3$, may rise 2-3 fold, as you found, for low doses, finally decreases to $10^2$-$10^3$/ml so that one can count plaques and transductions (Gal+, but Fla+ also tested) on the same plates. The transducees remain sensitive to 22B. Waiting for your records on 22.

X-ray: 200,000 r (sic) gives about 10% survival of phage, ca. 30% of FA (not very accurate). There may be a rise with smaller doses, but these experiments are not very promising in view of the tremendous doses needed throughout, and the small effects.

Lwoff effect. LT-22 and LT-2(22) not very promising. SW-543(22B) works reasonably well (lysates to $10^{10}$) This phage behaves in the same fashion as 22B grown on sensitive 543 in transductions of Gal+ and Fla+ H$_1$ or b.

Lysogenization: you have the data in my letter of 12/12. Another point: As in K-12 and lambda, infected LT-2 or 543 give rise to mixed or contaminated colonies. As far as we can tell now, the transductions are not mixed for lysogenicity. Esther has done a very clean experiment with lambda-transduction, with a comparable result. I would conclude that a transduction is, ordinarily, only that part of a progeny of an infected cell which has become lysogenic. This makes sense only in terms of segregation, presumably nuclear. A very useful new tool has just come up. In platings of PLT22 on LT2 a clear plaque was noticed, which, purified gave rise to a new phage we call 22V. 22V lyses LT2 almost completely-- ca. .1% survival in one expt., mostly rough, no lysogenic survivors so far-- but LT2(22) is resistant. An experiment a la Burnet&Lush worked beautifully. Adding $10^8$ PLT-22 to $10^7$ LT-2, followed after 15 minutes by excess 22V gave $10^8$ lysogenic survivors. This should make it possible to determine whether the particles in a prep. of PLT22 which transduce are the same as those which protect against 22V by inducing lysogenicity. 22V itself transduces to SW-435, but rather poorly. I haven't checked adsorption. It strikes me with some irony that I spent several weeks in'49 looking for such a phage or mutant for lambda, without success, and here this turns up of its own volition. Your letters

have repeatedly mentioned a lytic variant, but as I have already complained you kept the details in your own mind, and I had no telepathic access to them. I've gone over the letters, and still can't make out the story. Do you keep carbon copies? I would appreciate it if you could start from scratch about your interference experiment, the lytic variant, and the multiplicity experiment in your letter of 10/31. I shudder at the possibility that you may ask me to do likewise, but I will be glad to if I have inadvertently left out any essentials. We have to contend with the fact that unlike former days, your contexts are now no longer the same as mine, and we cannot communicate without being explicit.

On phase variation, I have to wait for some more suitable cultures from Edwards, to find a suitably stable diphasic I can use to test the role of the phase of the recipient cells in the transduction experiments.

Sincerely,

Joshua Lederberg

P.S. Do you want 22V, or do you already have it?